MULTI-OMIC PROFILING AS A PREDICTIVE TOOL FOR CHEMOTHERAPY-INDUCED COGNITIVE IMPAIRMENT

The Supportive Oncology Research Group

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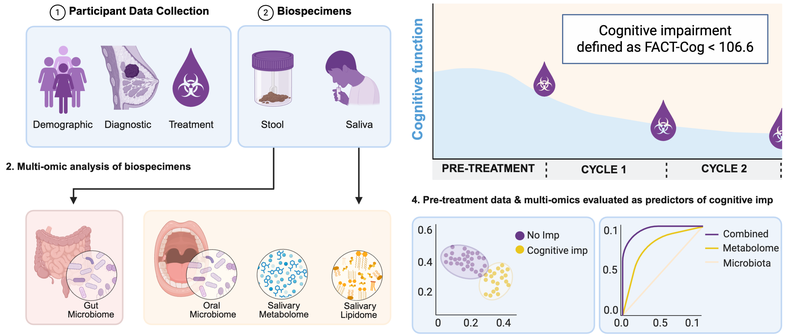
Introduction

- Chemotherapy-induced cognitive impairment (CICI) significantly impacts QoL, affecting peoples' ability to engage socially & professionally[1]
- CICI is heterogenous and highly unpredictable. As such management remains largely reactive in nature
- By integrating data from multiple biological sources, multi-omics models have gained increasing recognition for their risk predictive potential
- Despite progress in primary cancers, its utility in supportive care and side effect risk prediction remains unknown[2]

We compared the capability of pre-therapy multi-omics data to identify patients at risk of CICI

Methods



- Multi-omic profiling techniques included: 16S rRNA gene sequencing (microbiota) & LC-MS (metabolite & lipid acquisition)

Demographics

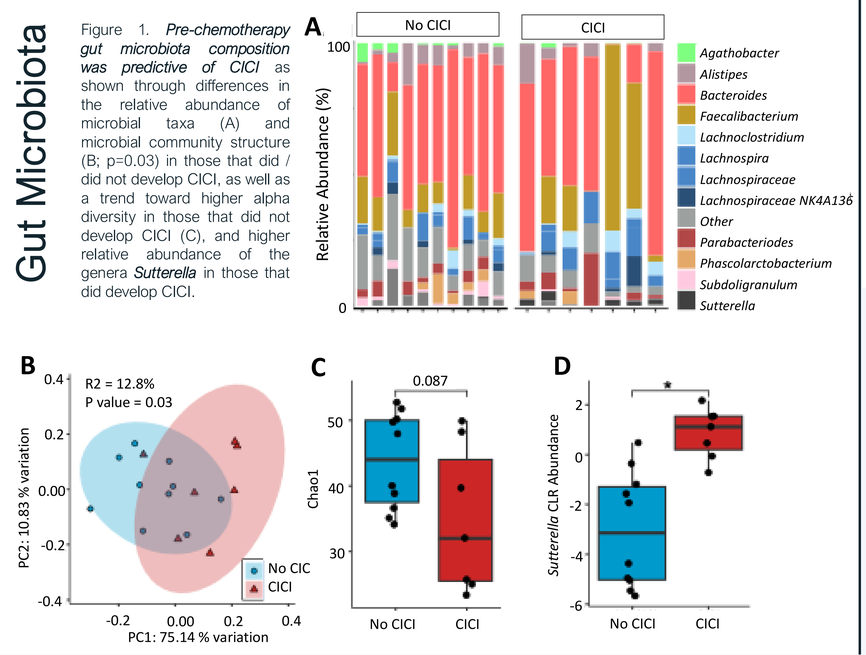
Participants (N = 20)			CICI (N = 8)	No CICI (N = 12)
Demographics	Age (mean ± SD)	56 ± 11.4	58 ± 5.0	55 ± 14.2
	BMI (mean ± SD)	30.6 ± 6.2	31.6 ± 5.2	30.1 ± 6.9
	Tobacco smoking, n (%)			
	Non-smoker	8 (40 %)	2 (25 %)	7 (58 %)
	Ex-smoker / Smoker	8 (40 %)	5 (62.5 %)	3 (25 %)
	Alcohol (# drinks / week), n (%)			
	≤10	13 (65 %)	6 (75 %)	7 (58 %)
	>10	3 (15 %)	1 (12.5 %)	2 (17 %)
Medical History	Mental health condition, n (%)			
	Yes	5 (25 %)	4 (50 %)	1 (8 %)
	No	13 (65 %)	3 (37.5 %)	10 (83 %)
	Antibiotics, n (%)			
	Yes	1 (5 %)	1 (12.5 %)	0 (0 %)
	No	16 (80 %)	6 (75 %)	10 (83 %)
	nd	3 (15 %)	1 (12.5 %)	2 (17 %)

Diagnosis & Treatment

Participants (N = 20)			CICI (N = 8)	No CICI (N = 12)
Diagnosis	Breast cancer stage, n (%)			
	Stage I	5 (25 %)	2 (25 %)	3 (25 %)
	Stage II	6 (30 %)	2 (25 %)	4 (33 %)
	Stage III	2 (10 %)	1 (12.5 %)	1 (8 %)
	Stage IV	1 (5 %)	1 (12.5 %)	0 (0 %)
	nd	6 (30 %)	2 (25 %)	4 (33 %)
	HER2 positive, n (%)			
	Yes	3 (15 %)	0 (0 %)	3 (25 %)
	No	15 (75 %)	7 (87.5 %)	8 (67 %)
	nd	2 (10 %)	1 (12.5 %)	1 (8 %)
	Hormone receptor positive, n (%)			
	Yes	13 (65 %)	6 (75 %)	7 (58 %)
	No	5 (25 %)	1 (12.5 %)	4 (33 %)
	nd	2 (10 %)	1 (12.5 %)	1 (8 %)
Treatment	Treatment type, n (%)			
	Neoadjuvant	7 (35 %)	3 (35.7 %)	4 (33 %)
	Adjuvant, following surgical resection	10 (50 %)	3 (37.5 %)	7 (58 %)
	nd	2 (10 %)	1 (12.5 %)	1 (8 %)
	Scheduled chemotherapy, n (%)			
	Doxorubicin & cyclophosphamide	11 (55 %)	4 (50 %)	7 (58 %)
	Paclitaxel	2 (10 %)	0 (0 %)	2 (17 %)
	Paclitaxel & carboplatin	4 (20 %)	2 (25 %)	2 (17 %)
	nd	3 (15 %)	2 (25 %)	1 (8 %)

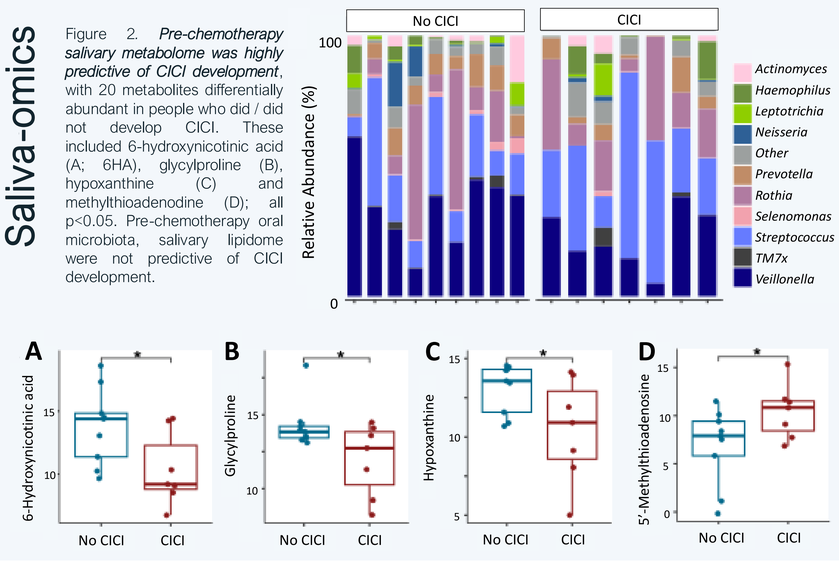
Gut Microbiota

Figure 1. *Pre-chemotherapy gut microbiota composition was predictive of CICI* as shown through differences in the relative abundance of microbial taxa (A) and microbial community structure (B; p=0.03) in those that did / did not develop CICI, as well as a trend toward higher alpha diversity in those that did not develop CICI (C), and higher relative abundance of the genera *Sutterella* in those that did develop CICI.



Saliva-omics

Figure 2. *Pre-chemotherapy salivary metabolome was highly predictive of CICI development*, with 20 metabolites differentially abundant in people who did / did not develop CICI. These included 6-hydroxynicotinic acid (A; 6HA), glycylproline (B), hypoxanthine (C) and methylthioadenodine (D); all p<0.05. Pre-chemotherapy oral microbiota, salivary lipidome were not predictive of CICI development.



Multi-omic Model

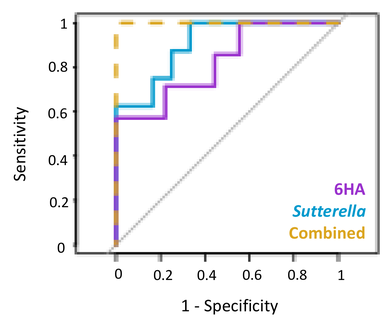


Figure 3. Integrating the top-ranked features of the pre-chemotherapy gut microbiota (i.e. *Sutterella* abundance, AUC = 91%) and salivary metabolome (i.e. 6HA, AUC = 83%), **increased predictive power** (AUC = 100%). *Sutterella* & 6HA were not significantly correlated (p=0.24).

To assess robustness, permutation testing was performed through randomly shuffling CICI labels and recalculating %AUC. Only 24 / 1000 iterations produced an AUC > 90%, suggesting observed predictive performance is **unlikely to have arisen by chance.**

Conclusions

- This study demonstrates the untapped potential of multi-omic profiling to identify pre-chemotherapy signatures associated with CICI
- Integrating gut microbiota and salivary metabolomic features enhance predictive power
- Larger, well-powered studies are needed to validate / refine predictive models and establish clinical utility of multi-omics in defining CICI risk
- Risk predictive models could enhance precision of supportive care

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References:

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2. Vasaikar et al. 2017. Nucleaic Acid Res